REMARKS

Claims 37, 45, 48, 53, 54, 72, and 75 to 78 and new Claim 80 are present for purposes of prosecution.

All of the above claims are rejected.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Amendments to Claims

Claims 37 and 72 have been amended so that after the starting daily dosage (250 mg/1.25 mg) the daily dosage range for metformin is -- from about 250 mg to about 750 mg --. Basis for the lower portion (250 mg) of the metformin daily dosages is found in the Specification at page 8, lines 20 to 24. In Claim 72, the maximum amount of glyburide (after the staring dosage) is 15 mg.

The daily dosage range for glyburide has been defined "from about 0.5 to about 15 mg" as previously present (as disclosed on page 9, lines 3 to 15 of the Specification).

Finally, as suggested by the Examiner, Claims 37 and 72, the only independent claims present, have been amended to indicate that the low dose combination of metformin and glyburide provides at least equivalent efficacy in treating patients with type 2 diabetes, but with reduced side effects, as compared to prior art combinations employed in higher doses, as claimed in original Claim 3.

Claim Rejections - 35 U.S.C. §112

Claims 37, 45, 48, 72, 75 to 78 and 80 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner contends that:

> "The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
>
> The claims in this application recite limitation, namely 'metformin...up to about 750mg' or 'metformin. . .at most about 750mg' and 'glyburide... up to about

15mg'. The examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the newly amended claims fail to find support in the original specification.

The scope of the instantly claimed range of metformin and glyburide encompasses any dosage amounts up to 750mg of metformin and up to 15mg of glyburide. For instance, 100mg of metformin and 0.1 mg of glyburide fall within the claimed dosage range of metformin and glyburide respectively.

The specification discloses that 'the low dose pharmaceutical formulation will be preferably be employed in first line therapy in a daily dosage to provide less than about 500 mg metformin per day, preferably no more than about 750mg metformin per day, preferably no more than about 500 mg metformin per day, and a starting dosage of from about 160 to about 500mg per day, preferably 250mg per day or 500 mg per day, in single or divided doses of one to four tablets daily' (page 8, lines 15-23); and that 'the glyburide is employed in starting daily dosage as low as about one-fifth of the starting daily dosage of glyburide employed in generally accepted medical practice....(that is a minimum starting daily dosage as low as 0.5mg)' (page 8, lines 24-29).

Therefore, it would have been clear to one skilled in the art, reading the instant disclosure, that the lowest daily dosages of metformin and glyburide required for this invention about 160mg and 0.5mg respectively.

As stated above, the ranges of daily dosage amount of metformin and glyburide introduced by the amendment, for example less than 160mg of metformin and less than 0.5mg of glyburide cannot be found in the specification and introduce new concepts and violate the description requirement of the first paragraph of 35 USC 112."

Claim 37 has been amended to make it clear that in accordance with Applicant's invention, metformin and glyburide are administered in a starting daily dosage of 250 mg metformin and 1.25 mg glyburide and, after the starting daily dosage, the daily dosage of metformin being from about 250 mg to about 750 mg per day, and the daily dosage of glyburide being from about 0.5 mg to about 15 mg per day.

Claim 72, with respect to the daily dosage of metformin, has been amended in a similar manner.

It is submitted that it is clear from the amended claims and the Specification that the starting daily dosage for metformin is 250 mg and thereafter from about 250 mg up to a daily maximum of

750 mg per day and the starting daily dosage of glyburide is 1.25 mg glyburide and thereafter from about 0.5 mg up to a maximum of 15 mg per day (page 8, lines 15 to 34 of the Specification).

In view of the above amendments, it is submitted that Claims 37, 45, 48, 72, 75 to 78 and 80 are in compliance with 35 U.S.C. §112, first paragraph.

Discussion of Invention

Applicant's invention as claimed is defined as a method for

1) first line treatment of diabetes

2) in a drug naïve patient

3) wherein a low dose of a combination of metformin and glyburide (starting dose of 250 mg metformin and 1.25 mg glyburide) in a weight ratio of 200:1 is administered

4) and after the starting dosage, the daily dosage of metformin is from about 250 mg to 750 mg

5) where the glyburide has a special particle size distribution of at most 25% of the particles are less than 11 μm and at most 25% are greater than 46 μm; thus the mean particle size of glyburide must be greater than ± 5 μm as disclosed by Bauer et al., and

6) where the low dose combination of metformin and glyburide provides at least substantially equivalent efficacy in treating type 2 diabetes in drug naïve patients, but with substantially reduced side effects, as compared to prior art combinations of metformin and glyburide employed in substantially higher daily doses.

The essence of Applicant's method is to employ a maximum daily dosage of 750 mg metformin together with the glyburide of special particle size distribution in a weight ratio of metformin:glyburide of about 200:1, to achieve equivalent efficacy as compared to efficacy achieved with prior art dosing that is more than 800 mg metformin/day, but with reduced side effects as compared to that observed with such prior art dosing. See page 41, lines 5 to 35 of the Specification.

In Applicant's method as claimed, use of the combination of the low dose formulation of metformin and glyburide (200:1 weight ratio) in first line therapy (at most 750 mg/day metformin) is safer (less side effects) than the use of higher doses (greater than 800 mg/day metformin), without substantial loss in efficacy. Applicant's invention as claimed resides in use of the low dose

formulation of 250 mg metformin / 1.25 mg glyburide to provide less than (or at most) 750 mg/day of metformin, in first line therapy, and which has essentially the same efficacy as the formulation containing 500 mg metformin / 2.5 mg glyburide which provides more than 800 mg/day, but use of the low dose formulation results in reduced side effects. Please note Figures 9 and 10 which show that use of the combination of 250 mg metformin / 1.25 mg glyburide results in substantially reduced side effects as compared to use of 500 mg metformin / 1.25 mg glyburide. See Figures 1 to 8 wherein it is shown that the use of low dose of 250 mg metformin / 1.25 mg glyburide provides essentially the same efficacy as use of the dose of 500 mg metformin / 2.5 mg glyburide. As will be seen hereafter, with regard to Figures 1 to 10, where the low dose metformin (250 mg) of the invention is used, the daily amount of metformin is less than (or at most) 750 mg while where the high dose of metformin (500 mg) is used, the daily amount of metformin is greater than 800 mg (prior art). This clearly demonstrates that Applicant's method as claimed which employs a low dose formulation to provide a daily dosage of metformin of at most 750 mg is patentable over methods of treating diabetes with higher doses of metformin in combination with glyburide.

Please note page 11 of the Specification starting at line 34 and continuing to page 12, line 20:

> "In carrying out the method of the invention employing the preferred starting low dose pharmaceutical formulation containing metformin and glyburide, to treat drug naive patients for diabetes, the efficacy in treating drug naive patients is at least substantially equivalent and incidence of side effects (gastrointestinal side effects and hypoglycemia) is surprisingly significantly and substantially reduced as compared to patients on higher daily dosages of metformin and glyburide (that is in starting dosages prescribed in generally accepted medical practice for treating diabetes). Thus, while efficacy in treating drug naive patients as measured by decrease in hemoglobin A_{1c} (HbA_{1c}) from baseline over time, decrease in fasting plasma glucose (FPG), increase in post-prandial insulin levels, and decrease in post-prandial glucose (PPG) excursion, are essentially substantially equivalent in the above-described patients when employing the low dose pharmaceutical formulation employed herein and substantially higher daily dosages, incidence of hypoglycemia and gastrointestinal side effects in drug naive patients treated with substantially higher daily dosages are substantially greater than in patients treated with the low dose pharmaceutical formulation."

It is submitted that Applicant's method as claimed is patentable over the combination of the cited Barelli et al. patent, Bauer et al. patent, *Drug Facts and Comparisons*, and Shell et al. patent.

Claim Rejections - 35 U.S.C. §103

Claims 37, 45, 48, 53, 54, 72, 75 to 78 and 80 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barelli et al. (WO 97/17975, publication date: May 22, 1997, equivalent to U.S. Patent No. 5,922,769) in view of Bauer et al. (U.S. Patent 5,258,185, issue date: November 2, 1993), *Drug Facts and Comparisons*, and further in view of Shell (U.S. Patent No. 6,340,475) basically for the same reasons set out in the March 13, 2008 Official Action. The previously cited Ohmura reference has been replaced with Shell et al. which the Examiner indicates that "Shell is being provided as a supplement reference to demonstrate the state of art knowledge in preparing metformin in various dosage forms including 125mg and 250 mg (Example 1)."

The Examiner further contends that:

> "With respect to the determination of metformin dosage being 250 mg and glyburide dosage being 1.25 mg, although Barelli et al. do not explicitly teach this particular dosage, Barelli et al. discloses 'the ratio 5mg of glibenclaimde+500mg of metformin, can be subdivided as desired, thereby having lower and/or fractional daily dosages thus allowing to treat the disease from its onset, as the glibenclaimde to metformin ratio, even when fractioned, will turn out to be very well balanced' (column 7, lines 58-63). Thus, one having ordinary skill in the art would have been motivated to determine optimum therapeutic combination dosage amounts of metformin and glyburide to treat drug naive patient, e.g., when 5mg of glibenclamide+500mg of metformin is subdivided into half (1/2) or quarter (1/4) amount, 2.5mg of glibenclamide and 250mg of metformin combination or 1.25mg of glibenclamide and 125mg of metformin combination can be prepared and used for the treatment of type II diabetes patient from its onset. Coupled with the above discussed dosage amounts intended for the treatment of the drug naive patient, one having ordinary skill in the art would have understood in light of Barelli (claims 1 and 2) that the weight ratio of meformin and glibenclaimde combination as long as maintained between 100: 1 to 200: 1 is useful for the treatment of type I1 diabetes from its onset.
>
> One having ordinary skill in the art would have understood in light Barelli that the subdivided and lower and/or fractional daily dosage of 5 mg of glibencamide+500 mg of metformin, for example 2.5mg of glibenclamide and 250mg of metformin combination or 1.25mg of glibenclamide and 125mg of metformin combination, or any fractions as long as maintained between 100: 1 and 200: 1, is useful for the less severe cases including diabetes patients from its onset (naive patient)."

Applicant respectfully disagrees with the Examiner's interpretation of the teachings of Barelli et al. at Column 7, lines 58 to 63. The key and essence of the Barelli et al. invention is using the metformin and glyburide in a 1:100 ratio. Barelli et al. clearly states in Column 2, lines 16 to 48 that formulations which have a 1:200 ratio do not obtain "optimum therapeutic effect due to the

quantitative unbalance of the medicaments in combination." Barelli et al. at Column 7, lines 58 to 63 discloses that

> "the ratio 5 mg of glibenclamide + 500 mg of metformin, can be subdivided as desired, thereby having lower and/or fractional daily dosages thus allowing to treat the disease from its onset, as the glibenclamide to metformin ratio, even when fractionalized, will turn out to be very well balanced."

One skilled in the art reading Barelli et al. at Column 7, lines 58 to 63 (absent the use of hindsight in view of Applicant's disclosure) can only come to one conclusion, namely that even when the 5 mg glyburide + 500 mg metformin are subdivided, the ratio of glyburide to metformin will always be 1:100 (to achieve the "well balanced") and not 1:200 since Barelli et al. clearly teaches that the 1:200 ratio is undesirable in that the 1:200 ratio does not produce "optimum therapeutic effect due to the quantitative unbalance of the medicaments in combination." (Barelli et al., Column 2, lines 16 to 41).

Thus, in effect, the Examiner is expanding the interpretation of Barelli et al. to cover undesirable combinations not contemplated by Barelli et al.

The Examiner further states that:

> "Furthermore, one having ordinary skill would have expected as taught by Barelli, Drug Facts and Comparisons (1995 Edition, pp. 547) and Shell combination that initiating therapy with low dose of 1.25 mg glyburide and 125mg or 250mg of metformin would be useful for the treatment of type 2 diabetes mellitus patient, especially for patients who are more sensitive to hypolgycemic drugs."

As indicated above, none of Barelli et al., *Drug Facts and Comparisons*, and Shell et al., each taken alone or in combination, discloses or suggests a method as claimed herein employing the combinations as claimed herein.

It is submitted that Applicant's invention as claimed is patentable over Barelli et al.

Barelli et al. disclose tablets containing a combination of 500 mg metformin and 5 mg glyburide for treating diabetes, so as to allow a daily dosage of 1500 mg metformin and 15 mg glyburide (column 2, lines 64 to 67), for maximum benefit, although such tablets may be subdivided. The Barelli et al. combination is 500 mg metformin / 5 mg glibenclamide or a 100:1 ratio to achieve good efficacy with minimal side effects.

Barelli et al. teach using a metformin:glyburide weight ratio of 100:1, whereas Applicant requires a ratio of 200:1.

Barelli et al. in Column 2 starting at line 16 continuing to line 41 teach that use of metformin in a weight ratio to glyburide of 200:1 results in a "quantitative unbalance of the medicaments in combination". Therefore, Barelli et al. use a ratio of 100:1. Thus, Barelli et al. teach away from use of Applicant's weight ratio of its low dose combination of metformin:glyburide of 200:1.

Barelli et al. has nothing to do with Applicant's inventive concept as claimed.

1) Applicant's method requires treating with a low dose combination of metformin (a maximum 750 mg daily) and glyburide.

Barelli et al. does not disclose or suggest using a low dose of metformin but teach using a daily dose of up to 1500 mg metformin. Until Applicant's invention, no one used a low dose of metformin, that is a maximum of 750 mg daily for treatment of diabetes. It therefore has to be presumed that Barelli et al. is not implicitly or otherwise suggesting to use a low dose of metformin, that is 750 mg or less, but apparently is suggesting to use more than 750 mg/day up to 1500 mg/day.

2) Barelli et al. makes no mention of particle size distribution of glyburide. Applicant's method requires a specific particle size distribution of glyburide not disclosed or suggested in Barelli et al.

3) Barelli et al. uses a weight ratio of metformin:glyburide of 100:1 and teaches that using a weight ratio of 200:1 (as does Applicant) is undesirable.

In the clinical study described in Columns 6 and 7 of Barelli et al., the patients treated were not drug naïve but were previously treated with combinations of metformin and glyburide as indicated at Column 7, lines 28 to 34.

Applicant has shown in working Example 3 that in accordance with the present invention use of a combination of 250 mg metformin and 1.25 mg glyburide to provide a metformin daily dose of less than 750 mg has reduced side effects and substantially equivalent efficacy as compared to a Barelli et al. combination of 500 mg metformin and 2.5 mg glyburide to provide a metformin daily dose of more than 800 mg. The fact that, in accordance with the present invention, use of a low dose combination of 250 mg metformin and 1.25 mg glyburide to provide a maximum daily dosage of 750 mg metformin has substantially equivalent efficacy of a Barelli et al.-like combination which

provides a daily dosage of greater than 800 mg metformin, while causing reduced side effects as compared to the Barelli et al.-like combination is, indeed, surprising and unexpected.

As seen in Example 3, Applicant has compared efficacy and safety of a combination of 250 mg metformin / 1.25 mg glyburide to provide at most 750 mg metformin/day versus efficacy and safety of a combination of 500 mg metformin / 2.5 mg glyburide to provide more than 800 mg metformin per day. The glyburide used in both compositions is the specially sized glyburide as claimed which is not disclosed or suggested by Barelli et al. The key to the invention is use of the combination to provide at most 750 mg metformin per day. The results obtained, namely reduced side effects and substantially equivalent efficacy, is indeed surprising and unexpected. It is indeed unobvious that using a combination to provide less metformin (less than 750 mg/day) would provide substantially equivalent efficacy but reduced side effects as compared to using a combination to provide more metformin (greater than 800 mg/day). This is surprising and unexpected.

See pages 36 and 37 (Example 3) of the Specification wherein it is stated as follows:

"**RESULTS**

The results obtained from the above studies indicate that the low dose metformin-glyburide (250/1.25) formulation of the invention achieved glycemic control at least essentially equivalent to the high dose metformin-glyburide (500/2.5) formulation as evidenced by

(1) a therapeutic response for hemoglobin A1c, namely, a reduction in HbA1c of below 7% (from a mean baseline of 8.2%) at week 20 (Figures 1, 2 and 3), at weeks 20 and 32 and final visit (Figures 4 and 5)

(2) a therapeutic response for fasting plasma glucose (FPG), namely, a reduction in FPG to less than 126 mg/dL after 20 weeks (from a baseline of about 175 mg/dL), (as shown in Figures 6)

(3) a therapeutic response for post-prandial insulin levels, namely an increase in post-prandial insulin of 19-25 μiu/mL (microinternational units/mL) (Figure 7)

(4) a therapeutic response for post-prandial glucose excursion (PPG) (that is the difference between post-prandial glucose and fast plasma glucose), namely, a decrease in post-prandial glucose excursion at week 20 of 17.7 for the 500/2.5 mg combo and 20.8 for the 250/1.25 mg combo versus 15.2 for metformin, 6.8 for glyburide. (Figures 8A and 8B).

At the same time, the above efficacy results employing the low dose formulation of the invention (Example 1) were achieved with reduced incidence of side effects (Figures 9 and 10).

As seen in Figure 9, the incidence of hypoglycemia employing the low dose formulation of the invention (Example 1) is less than about 1/3 of that occurring using the prior art high dose formulation (Example 2) employed in generally accepted medical practice for treating diabetes.

As seen in Figure 10, the incidence of gastrointestinal side effects employing the low dose formulation of the invention (Example 1) is less than 20% of that occurring using the high dose formulation (Example 2) employed in generally accepted medical practice for treating diabetes.

A discussion of the above results follows."

See pages 38 and 39 (Example 3) of the Specification wherein it is stated as follows:

"As first line therapy, a single formulation of fixed combination metformin/glyburide in ratio of a 200:1 metformin/glyburide was evaluated using two different dose strengths, a low dose (metformin/glyburide 250/1.25 mg) and a medium dose (metformin/glyburide 500/2.5 mg). The two dose strengths of fixed combination metformin/glyburide product were compared in a double-blind study to placebo, glyburide monotherapy and metformin monotherapy. Mean final doses achieved in each treatment arm were approximately 5.3 mg of glyburide [glyburide alone], 1307 mg of metformin [metformin alone], 557/2.78 mg [daily] of low dose (250/1.25 mg) metformin/glyburide fixed combination and 818/4.1 mg [daily] of medium dose (500/2.5 mg) fixed combination. When used as first line therapy, fixed combination metformin/glyburide treatment achieved statistically significant improvement in glycemic control compared to metformin, glyburide or placebo. The interim open-label treatment data confirmed the clinical utility of fixed combination therapy in a more 'glycemically diverse' patient population and for a longer period of time."

Thus, Applicant has presented comparative data which compares the formulation of the invention versus the closest prior art formulation.

In view of the above, it is quite clear that Applicant's method as claimed is neither disclosed nor suggested by Barelli et al. and thus is patentable over Barelli et al.

It is submitted that Applicant's invention is claimed as patentable over Bauer et al.

U.S. Patent No. 5,258,185 to Bauer et al. discloses in Col. 2, lines 17 to 20,

> "microionized, i.e. finely comminuted, glibenclamide (mean particle size ±5 μm) showed an improved drug release and bioavailability above all in the presence of tensides . . ."

There is no disclosure or suggestion in Bauer et al. of a method of treating diabetes in a drug naïve patient employing a low dose of a combination of metformin and glyburide. Bauer et al. discloses formulations containing glyburide but not metformin. In addition, the glyburide employed in Applicant's invention as claimed will have a mean particle size greater than ±5 μm.

Applicant's claim in Claims 37 and 72 glyburide having a particle size distribution so that at most 25% is less than 11 μm which means that at least 75% is greater than 11 μm. Claims 75 to 78 depend from Claim 37. Thus, all of the claims define a particle size range for glyburide of greater than ±5 μm. Accordingly, it is clear that Applicant's invention as claimed is patentable over Bauer et al.

It is submitted that Applicant's invention is claimed as patentable over the *Drug Facts and Comparisons* reference and Shell et al..

The *Drug Facts and Comparisons* reference and Shell et al. disclose doses of glyburide of 1.25 mg to 20 mg. However, there is no disclosure or suggestion in these references of combinations of glyburide and metformin, and the required ratios claimed herein.

Applicant's method as claimed is also patentable over a combination of Barelli et al., Bauer et al., *Drug Facts and Comparisons*, and Shell et al. As indicated, Barelli et al. does not disclose or suggest use of low dose metformin (250 to 750 mg daily). Barelli et al. is devoid of Applicant's inventive concept of use of a combination of low dose metformin (maximum daily dosage of 750 mg) and specially size glyburide employing a 200:1 weight ratio of metformin:glyburide. Even if Barelli et al. is taken with Bauer et al., *Drug Facts and Comparisons* and Shell et al. so that the Barelli et al. combination includes the Bauer et al. sized glyburide (which is different from Applicant's), the resulting combination would not make Applicant's method obvious since none of the references taken alone or in combination discloses or suggests use of low dose metformin (at most 750 mg/day) or treatment of drug naïve patients in first line therapy or use of specifically sized glyburide having a mean particle size of greater than ±5 μm in the 200:1 weight ratio which low dose combination is as efficacious as prior art higher dose combinations for treating diabetes but which causes reduced side effects as compared to prior art higher dose combinations. Furthermore, there is nothing in any of the cited references which would suggest to or motivate one skilled in the

art to make such a combination of references. Thus, the Examiner has not established a *prima facie* case of obviousness.

The Examiner further states that:

> "With respect to the recitation of claim 54 regarding measurements, those values are the same as those measured disclosed by Barelli et al. (column 4, lines 23-29)."

However, as indicated above, Barelli et al. is totally devoid of Applicant's inventive concept and does not make Applicant's method as claimed obvious.

The Examiner further maintains that:

> "With respect to the recitation of 'lowering blood glucose in a hyperglycemic human patient, decreasing insulin resistance, decreasing hemoglobinAlc, increasing post-prandial insulin levels or decreasing prandial glucose excursion' in claim 72, since the drug combination of metformin and glyburide is the same as what's disclosed in the prior art and are being administered to the same patient population, the recited effects are expected and thus do not limit the claims."

Again, none of the references taken alone or in combination disclose or suggest Applicant's method as claimed.

In the "Response to Arguments" section of the Official Action, the Examiner states that:

> "Applicant's argument in the response takes the position that Barelli does not disclose or suggest using a low dose of combination of metformin, particularly a maximum 750mg daily, and glyburide. Applicant asserts that Barelli actually teaches away from use of the applicant's weight ratio of its low dose combination of metformin:glyburide 200: 1. The applicant alleges that Barelli apparently is suggesting dose more than 750mg/day up to 1500mg/day.
>
> This argument is not found persuasive. Barelli teaches that 'the ratio 5mg of glibenclaimde+500mg of metformin, can be subdivided as desired, thereby having lower and/or fractional daily dosages thus allowing to treat the disease from its onset, as the glibenclaimde to metformin ratio, even when fractioned, will turn out to be very well balanced' (column 7, lines 58-63). Although Barelli discloses 100: 1 weight ratio as the specific embodiment, Barelli also teaches that a weight ratio higher than 100: 1 of metformin and glibenclamide combination including a weight ratio of 160:1 to 200:1 of metformin and glibenclamide combination is useful for the claimed invention (claims 1-2)."

Claims 1 and 2 of Barelli et al. relates to "treating diabetes in cases of secondary failure". Applicant's method as claimed is for first line treatment and not in cases of secondary failure. Thus, Claims 1 and 2 of Barelli et al. do not disclose or suggest Applicant's method as claimed.

The Examiner further states that:

> "Applicant's argument in the response takes the position that the resulting combination would not make Applicant's method obvious since none of the references taken alone or in combination discloses or suggests that the instant combination is as efficacious as prior art higher dose combinations for treating diabetes but which causes reduced side effects as compare to prior art higher dose combinations.
>
> This argument is not found persuasive. Unlike the applicant's argument, there is no indication in the instant claims that the administration of said combination must essentially treat diabetes as efficacious as prior art higher dose combination or reduce side effects as compared to prior art higher dose combinations. In other words, the objective evidence of nonobviousness is not commensurate in scope with the claims which evidence is offered to support. If the criticality of the instant invention is based on 'as efficacious as prior art higher dose combinations for treating diabetes but which causes reduced side effects as compare to prior art higher dose combinations' as the applicant alleged, such feature must be appeared in the claims so that the examiner give a preamble patentable weight. In absence of such critical element(s) in the claim, the examiner maintains the rejection of the record."

Claims 37 and 72 have been amended as suggested by the Examiner by combining each of Claims 37 and 72 with Claim 3 as originally claimed so that Claims 37 and 72 state that "wherein the low dose combination of metformin and glyburide provides at least substantially equivalent efficacy in treating type 2 diabetes in drug naïve patients, but with substantially reduced side effects as compared to prior art combinations of metformin and glyburide employed in substantially higher daily dosages."

In view of the above amendment to each of Claims 37 and 72, it is submitted that the rejection of Claims 37, 45, 48, 72, 75 to 78 and 80 should be withdrawn.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. The Examiner must meet three basic requirements to establish a *prima facie* case:

> "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP 2143."

See also In re Chu, 66 F.3d 292, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995); *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1444-1446 (Fed. Cir. 1992); and MPEP §2143. The burden of satisfying

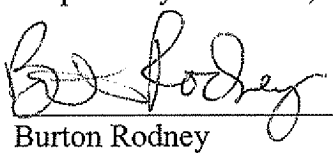
these requirements rests squarely with the PTO. *See Ex Parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Inter. 1986); MPEP §2142.

Here, these requirements are not met. There is no motivation in any of the cited references to combine Barelli et al., Bauer et al., *Drug Facts and Comparisons* and Shell et al., but rather, the Examiner has improperly employed hindsight to selectively combine parts of these references, using Applicant's disclosure. Additionally, there is no reasonable expectation of success in the prior art. Specifically, there is no reasonable expectation of success in the art for use of a low dose combination of metformin and glyburide (ratio of 200:1) in drug naïve patients to produce essentially equivalent efficacy but reduced side effects as compared to use of prior art high dose combination. As indicated, the prior art when combined does not teach or suggest all of the claim limitations.

As detailed hereinabove, Applicant has shown that a *prima facie* case of obviousness have not been established in the rejection of Claims 37, 45, 48, 53, 54, 75 to 78 and 80. However, even if the requirements for a *prima facie* obviousness case were satisfied, they have been rebutted herein.

In view of the foregoing, it is submitted that Claims 37, 45, 48, 53, 54, 75 to 78 and 80 overcome all formal objections and are patentable over all cited art taken in any combination and therefore are in condition for allowance.

Respectfully submitted,



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